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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/781,592	02/12/2001	Beverly M. Emerson	1211.003USI	1304

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EXAMINER

MARVICH, MARIA

ART UNIT PAPER NUMBER

1633

DATE MAILED: 02/22/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/781,592	Applicant(s) EMERSON, BEVERLY M.	
	Examiner Maria B. Marvich, PhD	Art Unit 1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 05 January 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 38,40,54-56,63,64,66,68,72-77,79-85,87 and 88 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 38,40, 54-56, 63,64,66,68,72-77,79-85,87 and 88 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

This office action is in response to an After-Final Amendment filed 1/5/06. **The amendment has been entered.** Claims 1-37, 39, 41-53, 57-62, 65, 67, 69-71, 78, 86 and 89-99 have been cancelled. Claims 38, 40, 54-56, 63, 64, 66, 68, 72-77, 79-85, 87 and 88 are pending in the application.

Upon further review of the instant claims and specification it is apparent that the application is not in condition for allowance. Therefore, prosecution is reopened. As new grounds of rejection are presented in this action that are not necessitated by applicant's amendment of the claims, this action is non-final.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 63, 64, 66, 68, 73, 74 and 87 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 69- 79 of copending Application No. 10/783,672. **This is a new rejection.**

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claims because the examined claim is either anticipated by, or would have been obvious over, the reference claims. Although the conflicting claims are not identical, they are not patentably distinct from each other because the cited claims of the instant invention are generic to all that is recited in claims 1-3 and 9-12 of US 10/783,672. That is, the cited claims of US 10/783,672 anticipate and fall entirely within the scope of the rejected claims of the instant application. Specifically, both sets of claims recite a method of identifying a compound that alters chromatin remodeling and that can also be detected by alteration of gene expression. Chromatin assembled DNA is contacted with SWI/SNF complexes and a transcription factor comprising zinc-fingers or leucine zippers.

Additionally, if a patent resulting from the instant claims was issued and transferred to an assignee different from the assignee holding the U.S. 10/783,672 application, then two different assignees would hold a patent to the claimed invention of U.S. 10/783,672 application, and thus improperly there would be possible harassment by multiple assignees.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 38, 40, 54-56, 63, 64, 66, 68, 72-77, 79-85, 87 and 88 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for identifying a compound *in vitro* that modulates direct interaction or modulates chromatin remodeling between mammalian SWI/SNF BRG1 complex with EKLF and GATA-1, does not reasonably provide enablement for identifying a compound *in vivo* or *in vitro* that modulates direct interaction or chromatin remodeling with any SWI/SNF chromatin remodeling complex and any DNA binding domain peptide. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. **This is a new rejection.**

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation (*United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is required is not based on a single factor but is rather a conclusion reached by weighing many factors (See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter, 1986) and *In re Wands*, 8USPQ2d 1400 (Fed. Cir. 1988); these factors include the following:

1) Nature of invention. The specification teaches that there is a need for high-throughput screening assays that identify small molecule compounds that enhance or block the

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association between chromatin remodeling complexes and the specific transcription factors with which they interact. These compounds could be used to treat disease associated with the transcription factors. The instant claims are drawn to a method of identifying compounds that modulate direct interaction between a SWI/SNF complex and a zinc-finger DNA binding domain peptide or chromatin remodeling mediated by a DNA binding a SWI/SNF complex and a DNA binding domain peptide.

2) Scope of the invention. Claim 38 recites that SWI/SNF complexes in direct interaction with zinc-finger peptides are contacted with a test compound and the amount of direct interaction between the two is measured. Claim 63 recites that a chromatin assembled DNA is contacted with SWI/SNF complexes and DNA binding domains and a test compound and the amount of chromatin remodeling is measured. An increase or decrease of either a direct interaction or chromatin remodeling is indication that the test compound modulates either the direct interaction or chromatin remodeling. The scope of the invention is broad in recitation of any SWI/SNF complex and in the claims drawn to chromatin remodeling any DNA binding domain peptide.

3) Number of working examples and guidance. The specification teaches chromatin remodeling is mediated by one of several complexes i.e. SWI/SNF, which are functionally and mechanistically distinct (page 3, line 7-22). The specification further states that the specificity of function is provided by its ability to interact directly with zinc-finger DNA –binding domains, which are mediated by BRG1, BAF155 and BAF170 and minimally BRG1 and BAF155. Using mammalian BRG1, applicants demonstrate that Sp-1, GATA-1 and EKLF can mediate transcription of a β -globin chromatin-assembled template *in vitro* in the presence of an E-RC1

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fraction concomitant with the generation of DNaseI hypersensitive sites. The β -globin promoter comprises binding sites for each of these transcription factors and E-RC1 comprises BRG1, BAF170, BAF155, BAF47 (see Armstrong, 1998, abstract). However, NF-kB and TFE-3 were not able to induce these changes. EKLF was also tested for its ability to induce transcription from the chromatin assembled HIV-1 promoter in an E-RC1 dependent fashion. GST pull down experiments and Western analysis were used to demonstrate that the interaction between EKLF or GATA or the zinc-finger domains of either and E-RC1 was direct. However, the zinc-finger DNA binding domains were insufficient to direct remodeling by E-RC1. The entire transcription factor was required for chromatin remodeling and transcriptional activation.

Applicants intend to identify compounds that inhibit or enhance the interaction of chromatin complexes and a domain of a protein by for example binding the SWI/SNF complex or the domain of the protein (see page 12, line 16-20). Furthermore, the specification teaches that these compounds can be administered to subjects (see page 14-18). For pharmaceutical screening, applicants propose identification of a direct interaction by the above steps. Then the protein is fluorescently labeled and added to a multiwell plate with zinc-finger motifs to allow direct interaction. Small molecule libraries are screened for the ability to disrupt the interactions. The specification teaches that the compounds that significantly increase or decrease zinc-finger interactions with SWI/SNF are the examined in *in vitro* chromatin remodeling and transcription assays and then tested in cultured cells and eventually used in animals and humans (see e.g. page 26-27). Finally, applicants propose prophetically that assembled p53 binding sites into chromatin structures could be used to identify compounds the modulate interaction with protein interaction at the chromosomal sites.

4) State of the art. Chromatin remodeling complexes are responsible for destabilizing nucleosomes as a means of regulating transcriptional activity of a chromosomal unit and can be monitored by DNase I digestion. Muchardt et al (1999) teach that the SWI/SNF chromatin remodeling complexes are found from yeast to man (Table 1) and comprise a core protein associated with about 10 subunits each (Nie, page 8879, col 2, paragraph 2). In humans, the core protein is of two types called BRG1 and hBRM. Interactions between ER, GR and PR and BRG1 have been detected using yeast two-hybrid analysis (Muchardt et al, 1999, page 192, col 2, paragraph 1). Each of these proteins comprises zinc finger DNA binding domains. Ichinose et al teach that specific interactions of ER and hBRM and BRG1 in yeast occur between the AF-2 activation domain in animals and the ligand-binding domain in yeast. Applicants have demonstrated in the instant specification that the zinc-finger DNA binding domain of EKLF and GATA-1 interact directly with BRG1. And as well, truncations of these proteins resulting in just the zinc-finger domain are also able to interact.

At the time of filing, the association of SWI/SNF complexes had been detected but the nature of the interactions was controversial. Wallberg et al teach that the mechanisms of recruitment of SWI/SNF to promoters may be through acidic activators and demonstrate that GR interacts in yeast through a domain within its activation domain. Muchardt et al and Ichinose et al teach that GR, PR and ER interact with BRG1 in a ligand dependent manner but the molecular mechanism that allows the cooperation is unclear (see e.g. page 192, col 2, Muchardt). DiRenzo et al teach that GR signaling is activated by BRG-1 and hBrm through Rb interaction with these molecules (page 7542, col 1). However, the association of the chromatin remodeling complexes with the nuclear factors was unclear. Post-filing art demonstrates that the actual interactions

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between transcription factors and chromatin-remodeling complexes are quite variable (see e.g. Debril et al, bridging paragraph 16677-16678).

5) Unpredictability of the art. The MPEP teaches, “However, claims reading on significant numbers of inoperative embodiments would render claims non-enabled when the specification does not clearly identify the operative embodiments and undue experimentation is involved in determining those that are operative. *Atlas Powder Co. v. E.I. duPont de Nemours & Co.*, 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984); *In re Cook*, 439 F.2d 730, 735, 169 USPQ 298, 302 (CCPA 1971). (see MPEP 2164.08(b). Applicants recite a method of identifying compounds that modulate a direct interaction between any zinc-finger domain peptide and any SWI/SNF complex. As well, applicants recite a method of identifying compounds that modulate chromatin remodeling by any DNA binding domain and any SWI/SNF complex.

1) Applicants have stated that GATA-1, Sp-1 and EKLF individually are able to activate transcription and remodel the chromatin from a β -globin promoter in the presence of ERC-1. However, only EKLF and GATA-1 were shown to interact directly with ERC-1 and the specific interaction was found to require BRG1 and BAF155. The significance of this interaction on transcription activation was only demonstrated by EKLF, which was able to activate transcription in the presence of BRG1/BAF155 and BAF170 in a zinc-finger dependent manner. Hence, applicants have only demonstrated the operability of the invention with two zinc-finger proteins. While the art teaches that at the time of filing, an association or cooperation between several DNA binding proteins was known, the exact nature of the interactions between chromatin remodeling complexes is quite complicated and controversial. DiRenzo teaches that the

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interaction between BRG1 and ER may actually be mediated by additional factors and not by BRG1 (see page 7548, col 1, paragraph 2). DiRenzo teaches that previous filings teaching interactions between GR, ER and PR and BRG1 were performed by yeast two-hybrid analysis, which is in conflict with their data. DiRenzo argues that the difference in results may be due to the different methods used. While they detected interaction by GST pull down experiments, the art used yeast two-hybrid analysis and this method either cannot distinguish between BRG1 and the additional endogenous factors or detects methods of interaction specific for yeast. Hence it is highly unpredictable that any zinc-finger containing protein will mediate chromatin remodeling through direct interaction with either BRG1 or any other SWI/SNF component without undue experimentation to identify the components and the nature of the interaction.

2) The method recites use of a zinc-finger DAN binding peptide or a DNA binding peptide. However the specification teaches that use of the zinc-finger domain alone could not modulate chromatin remodeling (see instant spec, page 21, line 29-31) but required the entire EKLF protein. Hence the DNA binding peptides have not been demonstrated to be sufficient model system for chromatin remodeling. A method of identifying compounds that modulate chromatin remodeling would require the entire transcription factor. Absent this, the significance of the interaction would be unpredictable.

6) Amount of Experimentation Required. Given the unpredictability of the art, the poorly developed state of the art with regard to predicting the structural/ functional requirements of interactions, the lack of examples reflecting the genus of recited interactions and the lack of guidance provided by applicants, the skilled artisan would have to have conducted undue, unpredictable experimentation to practice the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 38, 40, 54, 63, 64, 66, 68, 72-77, 79, 80, 83, 84, 87 and 88 are rejected under 35 U.S.C. 102(b) as being anticipated by Armstrong et al, Cell, 1998, page 93-104. **This is a new rejection.**

Armstrong et al teach a method of compounds that modulate the binding of EKLF with ERC-1, which comprises several chromatin-remodeling subunits of SWI/SNF (BRG1, BAF170, BAF155). The method involves providing ERC-1, which comprises a subunit of SWI/SNF and EKLF, which is a transcription factor that comprises a zinc-finger DNA binding domain. Additionally, the complex is incubated in the presence of apyrase (see e.g. figure 2). An increase or decrease in chromatin remodeling is assayed by measuring DnaseI sensitivity, which also reflects an increase or decrease in interaction between ERC-1 and EKLF as recited in claim 38, 40, 54, 63, 66, 68, 72, 75-77, 79, 80, 83 and 88. The chromatin is part of β -globin promoter as recited in claim 64. Transcriptional activity can also be monitored (see e.g. figure 3) as recited in claim 87.

Conclusion

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No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria B. Marvich, PhD whose telephone number is (571)-272-0774. The examiner can normally be reached on M-F (6:30-3:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, David Nguyen, PhD can be reached on (571)-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Maria B Marvich, PhD
Examiner
Art Unit 1633

February 1, 2006

DAVETRONG NGUYEN
SUPERVISOR/EXAMINER

